Osteoporosis

Definition of Osteoporosis

Osteoporosis, or porous bone, is a disease in which bone tissue is normally mineralized but the mass or the density of the bone is decreased and the structural integrity of trabecular bone is impaired.

Types of Osteoporosis

1. Postmenopausal or primary osteoporosis

Postmenopausal osteoporosis occurs in the middle-aged and older women. It can occur due to estrogen deficiency as well as estrogen –independent age-related mechanisms. Hormonal deficiency also can increase with stress, excessive exercise, and low body weight. Postmenopausal changes include a substantial increase in bone turnover, which, an imbalance between the remodeling activity of osteoclasts and osteoblasts. Sex hormones, especially estrogen and testosterone, are significant in premenopausal bone maintenance, however, when estrogen levels drop after menopause; it appears that circulating androgens become significant effectors on bone metabolism. Poor nutrition and insufficient intake or malabsorption of dietary minerals, including calcium is factors in the development of osteoporosis. Calcium absorption form the intestine decreases with age, and studies of individuals with osteoporosis show that their calcium intake is lower than that of age-matched controls. Deficiencies of vitamins, particularly vitamins C,D, E and K, also contribute to bone loss.

2. Secondary osteoporosis

Secondary osteoporosis is caused by hormonal imbalances (endocrine disease, diabetes, hyperparathyroidism, hyperthyroidism), medications (such as heparin, corticosteroids, phenythoin, barbiturates, lithium), and other substances (including tobacco and ethanol). Other conditions include rheumatoid disease, human immunodeficiency virus (HIV), malignancies, malabsorption syndromes, liver or kidney disease; also increase the risk for developing osteoporosis. Secondary osteoporosis sometimes develops temporarily in individuals receiving large doses of heparin. Heparin promotes bone resorption by decreasing collagen synthesis or by increasing collagen breakdown. Another form of transient osteoporosis of the hip is associated with the third trimester of pregnancy or the immediate postpartum period.

Pathophysiology

Osteoporosis develops when the remodeling cycling or the process of bone resorption and bone formation is disrupted leading to an imbalance in the coupling process. The explosion of the new information in field of bone biology has led to new understanding of the roles of hormones, growth, and signaling factors, and cellular biology in osteoporosis.

The osteoclast differentiation pathway is directed by a series of processes that include proliferation, differentiation, fusion and activation. These processes are controlled by hormones, cytokines, and paracrine stromal-cell microenvironment interactions. Therefore the intercellular communication in bone and the key molecular regulators are necessary for bone homeostatis. Certain transcript factors known as Forkhead box (FoxO) help protect against the effects of OS by preventing excess accumulation of ROS and regulating certain genes that affect DNA repair and cell life span. Normal bone homeostasis is dependent on the balance between the cytokine receptor activator of nuclear factor, ligand (RANKL), its receptor RANK, and its decoy receptor osteoprotegerin (OPG); understanding this has lead to a tremendously increased knowledge of osteoclast biology and pathogenesis of bone loss.

Postmenopausal osteoporosis is characterized by increased bone resorption relative to the rate of bone formation, leading to sustained bone loss resulting from estrogen deficiency. Bone loss resulting from estrogen deficiency also contributes to osteoporosis in men.

Sex steroids exert anti-apototic effects on osteoblasts but exert pro-apoptotic effects on osteoclasts; in both scenarios this is accomplished by activating the extracellular signal regulated kinases (ERKs). Estrogen activates ERKs outside the nucleus; ERKs then accumulate in the nucleus and activate downstream transcription factors.

Glutocorticoid induced osteoporosis is characterized by increased bone resorption and decreased bon formation. Glucocorticoids increase RNKL expression and inhibit OPG production by osteoblasts. The use of immunosuppressive drugs such as cyclosporine A, to reduce refection of transplanted organs also alters the OPG/RANKL RANK system and can lead to postransplantation osteoporosis.

Age related bone loss begins in the third to fourth decade. The cause remains unclear, but it is known that decreased serum growth hormone and IGF levels along with increased binding of RANKL and decreased OPG affect osteoblast and osteoclast function. Los of trabecular bone in men proceeds in a linear fashion, with thinning of trabecular bone rather than complete loss as is noted in women.

Genetics

In recent years there has been progress made in studies understanding the genetic basis to osteoporosis. Genetic factors that contribute to osteoporosis by influencing not only bone but mineral density but also bone size, bone quality and bone turnover. Meta-analysis has been used to define the role of several candidate genes in osteoporosis. Some qualitative trait loci that regulate bone mass identified by linkage studies in humans and experimental animals have been replicated in multiple populations. Genes that cause monogenic bone diseases also contribute to regulation of bone mass in normal population. Genome wide association studies and functional genomics approaches have recently begun to apply to genetic studies of osteoporosis.

* Family history
* White/Asian Race
* Increased Age
* Female Gender

Epidemiology

* 200 million people worldwide suffer from osteoporosis
* Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe.
* At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their lifetime.
* An increased risk of 86% for any fracture has been demonstrated in people that have already sustained a fracture.
* Fewer than 10% of vertebral fracture results in hospitalization even if they cause pain and substantial loss of quality of life.
* In Europe, the prevalence defined by radiological criteria increases with age in both sexes and is almost as high in men as in women: 12% in females (range 6-21%) and 12% in males (range 8-20%).
* Hip fracture rates are more common in Scandinavian and North American than these observed in Southern European, Asian and Latin American Countries.
* In women over 45 years of age, osteoporosis accounts for more days in the hospital than any other diseases, including diabetes, myocardial infarction and breast cancer.
* In Sweden, osteoporotic fracture in men account for more hospital bed days than those due to prostate cancer.
* By 2050, the worldwide incidence of hip fracture in men is projected to increase by 240% in women and 310% in men.
* The estimated number of hip fractures worldwide will rise from 1.66 million in 1990 to 6.26 million in 2050, even if age-adjusted incidence rates remain stable.

Disease Described

Disorders of Bone

Metabolic Bone Disease is characterized by abnormal bone structure that is caused by altered or inadequate biochemical reactions resulting in disorders of bone strength. Abnormalities include genetic, mineral, vitamin, and structural abnormalities.

Signs and Symptoms

Clinical manifestations of osteoporosis depend on the bones involved. The most common is bone deformity. Pain tends to occur only when there is a fragility fracture. Fractures are likely to occur because of the trabeculae of spongy bone become thin and sparse and compact bone becomes porous. As the bones lose volume, they become brittle and weak and may collapse or become misshapen. Vertebral collapse causes kyphosis and diminished height. Fracture of long bones particularly the femur and hummers, distal radius, ribs, and vertebrae are most common. The most serious fractures are hip fractures because of their resultant chronic pain, disability, diminished quality of life, and premature death. Fatal complications of fractures include fat or pulmonary embolism, hemorrhage, and shock

Diagnosis

The World Health Organization has defined osteoporosis based on bone density. Normal bone mass is greater than 833 mg/cm2. Osteopenia or decreased bone mass is 833 to 648 mg/cm2. Osteoporosis is bone mass less than 648 mg/cm2.

[**DEXA Scan (Dual X-ray Absorptiometry)**](http://www.webmd.com/osteoporosis/guide/dexa-scan)

The most common osteoporosis test is dual X-ray absorptiometry -- also called DXA or DEXA. It measures people’s spine, hip, or total body bone density to help gauge fracture risk. Read more.

[**Beyond DEXA: Other Bone Mineral Density Tests**](http://www.webmd.com/osteoporosis/guide/beyond-dexa)

Various methods can check bone density, including ultrasound and quantitative computed tomography (QCT). Bone density scores and cost may vary by testing method.

Continue reading below...

[**Blood Test Markers**](http://www.webmd.com/osteoporosis/guide/know-your-osteoporosis-blood-test-markers)

Whether you're being screened or treated for osteoporosis, your doctor may order a blood or urine test to see the metabolism of bone. This provides clues to the progression of your disease.

[**Bone Densitometry**](http://www.webmd.com/osteoporosis/guide/bone-densitometry)

Bone densitometry is a test like an X-ray that quickly and accurately measures the density of bone.

Treatment

Treatment is more common and is focused on preventing fractures and maintaining optimal bone function. The role of calcium intake to prevent and treat osteoporosis is controversial. It is well accepted that oral calcium intake sufficient to maintain normal calcium balance is necessary during adolescence to ensure development of peak bone mass and that calcium-deficient diets can aggravate bone loss associated with menopause and aging. Recommendations have been established for young women of 1000 mg of calcium daily and for postmenopausal women of 1500 mg daily with vitamin D. Other nutrients that appear to have a positive impact on bone health include magnesium, Vitamin K and docosahexaenoic acid or DHA.

Regular moderate weight bearing exercise can slow the rate of bone loss and in some cases reverse demineralization because the mechanical stress of exercise stimulates bone formation. An exercise program can enhance muscle strength as well.

Biophosphonates are a class of inorganic pyrophosphate derivatives that bind bone mineral and improve osteoblast and osteocyte survival while promoting osteoclast apoptosis, thus slowing the bone remodeling process. Another treatment is the use of denosumab, a monoclonal antibody that bines the cytokine receptor activator of RANKL. RANKL inhibition blocks the maturation, function, and survival of osteoclasts, thus reducing bone resorption.

Teriparatide also called PTH 1-34 is a biosynthetic form of parathormone and contains the first 34 amino acids of parathyroid hormone. Given subcutaneous injection, PTH reduces vertebral fractures but use I limited to a period of 24 months because the development of osteosarcoma.

**Medicines Approved to Prevent and/or Treat Osteoporosis**

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| --- | --- | --- | --- |
| Class and Drug | Brand Name | Form | Frequency |
| Bisphosphonates | | | |
| Alendronate | Generic Alendronate and Fosamax® | Oral (tablet) | Daily/Weekly |
| Alendronate | Fosamax Plus D™ (with 2,800 IU or 5,600 IU of Vitamin D3) | Oral (tablet) | Weekly |
| Ibandronate | Boniva® | Oral (tablet) | Monthly |
| Ibandronate | Boniva® | Intravenous (IV) injection | Four Times per Year |
| Risedronate | Actonel® | Oral (tablet) | Daily/Weekly/Twice Monthly/Monthly |
| Risedronate | Actonel® with Calcium | Oral (tablet) | Weekly |
| Risedronate | Atelvia TM | Oral (tablet) | Weekly |
| Zoledronic Acid | Reclast® | Intravenous (IV) infusion | One Time per Year/Once every two years |
| Calcitonin | | | |
| Calcitonin | Fortical® | Nasal spray | Daily |
| Calcitonin | Miacalcin® | Nasal spray | Daily |
| Calcitonin | Miacalcin® | Injection | Varies |
| Estrogen\* | | | |
| Estrogen | Multiple Brands | Oral (tablet) | Daily |
| Estrogen | Multiple Brands | Transdermal (skin patch) | Twice Weekly/Weekly |
| Estrogen Agonists/Antagonists Also called Selective Estrogen Receptor Modulators (SERMs) | | | |
| Raloxifene | Evista® | Oral (tablet) | Daily |
| Parathyroid Hormone | | | |
| Teriparatide | Forteo® | Injection | Daily |
| RANK ligand (RANKL) inhibitor | | | |
| Denosumab | ProliaTM | Injection | Every 6 Months |

\*Estrogen is also available in other preparations including a vaginal ring, as a cream, by injection and as an oral tablet taken sublingually (under the tongue). The vaginal preparations do not provide much bone protection.

References

*International Osteoporosis Foundation*. (2014, January). Retrieved from www.iofbonehealth.org

McCance, K. H. (2014). Pathophysiology The Biologic Basis for Disease in Adults and Children. St Louis, Missouri: Elsevier Mosby.

*National Osteoporosis Foundation*. (2014, January). Retrieved from wwwnof.org

Uitterlinden, A. v. (2006). Identifying genetic risk factors for osteoporosis. *Musculosketal Neuronal Interact*, (6)1:16-26.

*World Health Organization* . (2014, January). Retrieved from World Health Organization - Osteoporosis : www.who.org